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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/530,935	Applicant(s) HEARING ET AL.	
	Examiner Christopher Drabik	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-20 is/are pending in the application.

4a) Of the above claim(s) 20 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-19 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in response to this action, to elect a single invention to which the claims must be restricted.

Group I: claims 1-19, drawn to a method of regulating adenovirus packaging, packaging sequences thereto and method for treating patients using adenoviral vectors.

Group II, claim 20, drawn to a composition comprising a P-complex.

The special technical feature of group I is a method of modifying adenoviral vectors such that packaging might be repressed. The special technical feature of group II is an incompletely defined protein complex apparently involved in adenoviral packaging.

Pursuant to a telephonic interview with Dorothy Auth on June 20, 2001, Group I was elected for examination. Accordingly Claims 1-19 are examined herein and Claim 20 is withdrawn.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9 and 19 rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Claim 9 recites "...administering an adenovirus vector that was prepared using the vector of claim 8..." Claim 19 recites "...administering an adenovirus vector that was prepared using the vector of claim 18..." Claims 8 and18 are product claims with no method steps or claims for intended use. The steps required for the preparation of the virus to be used in claim 9 or 19 are not provided.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 5 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of regulating adenoviral packaging wherein repression involves the binding of the lac repressor or COUP-TF protein, does not reasonably provide enablement for the repression of packaging caused by other DNA binding proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

For enablement purposes, "repressor" is taken to mean repressor of packaging which binds specifically to it's cognate sequence. However, the scope of the claims might encompass any adenovirus binding agent, specific or non-specific, which reduces the encapsidation of virus. For written description purposes, non-specific agents are not disclosed sufficiently to enable those embodiments of the invention. The scope of the claims encompasses any eukaryotic or prokaryotic protein and protein binding sight which acts to reduce packaging. The scope of the claims further encompasses any vector containing the packaging/repression

Claims 1-5 are drawn to a method of repressing the packaging of adenovirus wherein repression is mediated by the binding of a DNA binding protein to elements involved in packaging. Applicants have defined elements in the 5' region of the

adenovirus 5 genome which direct packaging and have demonstrated that virus production is decreased in cells which have been co-transfected with an adenoviral vector and a construct expressing the repressor protein. Applicants have defined adenovirus A – elements I-VI. Each of the elements has the in vitro capability of binding COUP-TF, albeit with different specificity. (see also applicant's paper: Schmid et al (1998) Journal of Virology Vol 72, No 8: 6339 –6347, see espacially page 6344 1st column, end of paragraph bridging 6343-44) Interestingly, there is an inverse correlation between the in vitro binding affinity of COUP-TF to A elements and the apparent ability of the A elements to direct packaging. Cell culture experiments involving adenovirus vectors engineered to contain packaging elements of hexamer or greater repeats of single types of A elements lead to the applicant's conclusion that the A-I element was the most efficient at directing packaging, whereas, A-VI was the least efficient. Conversely, COUP-TF binds with the highest affinity to A-VI and the least affinity to A-I.

Prospectively the applicants have suggested that any DNA binding protein might be used in the system as described, however, examples have been only provided with regards to two DNA binding proteins. A significant structural aspect of the protein - DNA interaction with regard to enablement of other embodiments of the claimed invention is that both exemplified proteins overlap the packaging sequence either completely (COUP-TF) or partially (lac). It is apparent that a limitation of the system is that the protein responsible for repressing packaging must at least partially occlude the packaging sequence. A significant aspect of unpredictability exists when combining

sequences of disparate functionality. This unpredictability is demonstrated aptly by the applicants in showing that engineered packaging sequences vary widely in their ability to function as designed. For example, there is a large disparity in the fold-repression in comparing the optimal COUP-TF construct and the provided lac construct. Also it is obvious that a good deal of optimization is required to achieve high levels of packaging in repression even with the two proteins demonstrated. Applicants point to a hierarchy of functional importance (see pages 33 and 34) which apparently involved a good deal of trial and error experimentation. Applicants provide little guidance in determining how the packaging signal could be configured to accommodate other packaging repressor proteins and have not demonstrated that other proteins would work in the system. The disclosure provides no rationale for using one A element construct containing 12 packaging sequence repeats over a second A element construct with only two repeats. Apparently the number of repeats are important for the proper functioning of the invention, however, applicants have not provided guidance regarding how one of skill in the art might determine this number. Applicants have provided no guidance with regard to establishing which packaging elements configuration would function best with which DNA binding protein other than for lac and COUP-TF which happen to overlap the packaging sequence.

Given the disparity in the two DNA binding elements with regard to packaging repression, applicants ability to predict the efficiency of other constructs with different DNA binding proteins seems questionable. Also assuming the structural requirement that the packaging repression motif overlap with packaging element it is unclear from

the disclosure what other DNA binding proteins might function in the system as claimed. With regard to enablement of claim 17 in which applicants claim an adenoviral system comprising an E2F repressor binding site, 35 USC 112 1st paragraph is clear in stating that for an invention to be enabled, both how to make and use must be clearly provided by applicant. Considering the foregoing discussion, it is unclear to the examiner that use of the construct has been enabled based on the amount of experimentation required for optimization of e.g number of sequence repeats, the apparent differences in repression of different proteins and the lack of guidance provided for the use of other DNA binding proteins. Without a demonstration of the functionality of other elements which predictably and uniformly function to repress packaging, it is unclear whether the scope of the invention regarding any DNA binding protein and any form of packaging element modification is enabled. Given the limitations of the packaging element with regard to engineering DNA binding sites, the unpredictability of repression as demonstrated by the disparity of the two examples provided, the limited guidance in designing DNA modules which would satisfy the scope of the claimed invention, it would require undue experimentation for one of skill in the art to practice the full scope of the invention as claimed.

Claim 9 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 9 and 19 are drawn to methods of therapeutic

intervention based upon the transfer of a nucleic acids encoding a protein. The scope of the claims are broad in that no particular disease state is claimed, no method of adminsitration is recited and no specific adenoviral construct is described.

The factors to be considered in determining enablement are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation....Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Factors that can be used in evaluating undue experimentation include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

As claims encompassing gene therapy these inventions are anticipatory of a treatment which alleviates a disease state. Gene therapy as a means for curing or alleviating human disease states remains incompletely proven and unpredictable. Verma et al. In reviewing the art of gene therapy writes: "Although more than two hundred clinical trials are currently underway... there is still no single outcome that we can point to as a success story" (see Verma et al., page 239, col. 1). More recently, Patterson, directing remarks to the Senate subcommittee on Public Health stated :"To date more than 4000 patients have participated in gene therapy studies (in 372 NIH

registered trials)... Only one percent of the trials (3 protocols) have progressed to phase III efficacy studies. Thus, most human gene therapy clinical trials have been focused on safety rather than efficacy. For this reason, *it is perhaps more appropriate to refer to this technology as gene "transfer" rather than 'gene therapy', until there is more evidence for the therapeutic benefit of this technology."* (Patterson A (2000) http://www4.od.nih.gov/oba/patterson2-00.pdf see page 2, 2nd full paragraph).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al. explains, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated. [See Eck et al Gene-Based Therapy in *The Pharmaceutical Basis of Therapeutics*, *9th ed* (1996) McGraw Hill ¶ bridging pages 81-82.]

Specifically with regard to adenoviral vectors, immune responses poses a considerable problem for the long term expression of transgenes. Verma et al in reviewing the difficulties of adenoviral gene transfer write "...the immune system is behind the short term [transgene] expression that is usually obtained from adenoviral

vectors...The immune reaction is potent eliciting both the cell-killing 'cellular ' response and the antibody-producing 'humoral' response. " (Verma et al (1997)Nature 389: 239-242, see columns 1 and 2, page 241.) Indeed, it is well established in the art that adenoviruses elicit strong humoral and cellular immune responses. This is a significant hurdle to overcome, because attempts to achieve longer term expression of transgenes generally involve repeat administration of recombinant adenoviral vector. Second administrations of virus generally elicit increased immune responses leading to very inefficient gene transfer. Hence Wilson et al state "Most often the second administration of adenoviral vector is inefficient or impossible because of the cellular and humoral immune responses that mimic the immune response to any viral infection" (Wilson et al (1999) Adenovirus Vectors in *The Development of Gene Therapy*, Friedman, T ed. CSHL Press, Cold Spring Harbor, New York. see page 86). Verma et al conclude by stating "There are considerable immunological problems to be overcome before adenoviral vectors can be used to deliver genes and produce sustained expression." (p 241, second column)

Applicants have not provided any evidence suggesting that the hurdles to overcome in successfully practicing gene therapy have been resolved by the adenoviral vector of the instant application. The scope of the claims broadly encompasses the use of any heterologous gene to treat any disease. Applicants have not indicated which genes may be appropriate for specific disease states. While the scope encompasses the treatment of any disease state, no demonstration of a vector containing a therapeutic gene is disclosed and no in vitro or in vivo data is provided regarding the

ability to cure a specific disease state. Considering the nature of the invention, the unpredictable state of the art, the lack of guidance, and the lack of working examples, it would require undue experimentation for one of skill in the art to practice the invention as claimed,

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 6, 7, 10, 11, 12,13, 14, and 15 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Grable et al (Journal of Virology (1990) 64(5) 2047-2056). Claims 6-15 are drawn to adenoviral vectors containing packaging signal sequences and COUP-TF binding sequences. The central element of the packaging signal sequence claimed is 5'-TTGN$_8$GC-3' and is present in wild type adenovirus. COUP-TF is capable of binding all 6 A-elements of the Ad-5 packaging sequence (see Schmid et al Journal of Virology (1998), 72(8); 6339-6347) and, therefore, COUP-TF binding sites are also constituents of wild type virus.

Grable et al disclose the packaging signal sequence region of adenovirus 5. The signal sequence contains a "plurality" of COUP-TF binding sites (at least 5) and has 3 copies of the 5'-TTGN$_8$GC-3' motif (see page 2048, figure 2.) Hence the limitations of

claims 6,7 and 10 are clearly anticipated. Based on a minimal packaging sequence of 5'-TTGN_8GC-3', the adenovirus sequence disclosed by Grable et al has at least 3 packaging signal sequences and also contains COUP-TF binding sites which are embedded, flank, alternate or are between packaging signal sequences. Hence, claims 11, 12, 13, 14 and 15 are clearly anticipated by Grable et al.

Claim 8 and 18 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Haj-Ahmad et al. (Journal of Virology (1986) 57(1): 267-274

Claim 8 is drawn to an adenovirus vector comprising a packaging sequence COUP-TF binding sites and also a heterologous gene. As discussed above, both COUP-TF and 5'-TTGN_8GC-3' sequences are inherent to the Ad-5 packaging region. Haj-Ahmad describe the generation of an adenoviral vector (Ad-5) comprising the packaging sequence and also the thymidine kinase gene. Hence, the limitations of claim 8 are clearly anticipated by Haj-Ahmad.

Conclusion

Claims 2, 3 and 16 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 16 is deemed free of the prior art, given the unpredictability inherent in the process as discussed above, and the failure of the prior art to teach or reasonably suggest an adenoviral vector containing a lac repressor site.

Claims 1, 4, 5 -15, and 17-19 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Drabik whose telephone number is 703-605-1156. The examiner can normally be reached on Monday-Friday from 9am to 5pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on 703- 305-4051. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4242.

Inquiries of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234. Questions regarding review of formality issues may be directed to Kim Davis, the patent analyst assisting in this application. She may be reached at 703-305-3015.

Deborah Clark

DEBORAH J. R. CLARK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600